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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER
[illegible]

ART UNIT	PAPER NUMBER
[illegible]	[illegible]

DATE MAILED: [illegible]

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/386,266	Brayden
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *08/23/00.*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-6 and 15-20* ~~is~~/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-6 and 15-20* ~~is~~/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: _____

DETAILED ACTION

Applicant's Amendment

1) Acknowledgment is made of Applicant's amendment filed 08/23/00 (paper no. 6), which amendment has been entered.

Election

2) Acknowledgment is made of Applicant's election, without traverse, of invention I, claims 1-6 and 15-20, in response to the restriction requirement mailed 08/01/00 (paper no. 5).

Status of Claims

3) Claims 7-14 and 21-24 have been canceled via the amendment filed 08/23/00.

Claims 1-6 and 15-20 are pending and are under examination. An Action on the Merits for these claims is issued.

Drawings

4) The drawings submitted 06/31/99 are not objected to by the Draftsperson under 37 C.F.R 1.84 or 1.152 and as such, the drawings have been approved as formal drawings.

Priority

5) This application claims domestic priority to the provisional application, SN 60/098,760, filed 09/01/1998.

Specification - Informalities

6) The specification is objected to for the following reasons:

(a) The first paragraph of the specification does not provide information about the provisional application to which domestic priority is claimed. Correction is requested.

(b) The drawings 1 and 2 are objected to by the Examiner for improper labeling of the subparts or panels. Figures 2, 6, 9 and 10 have two panels, A and B; Figure 4 has three panels, 4A, 4B and 4C; and Figure 5 has four panels, 5A, 5B, 5C and 5D. These Figure panels should be labeled as Figure 2A and 2B and so on. The 'Brief Description of the Drawings' in the specification should refer to the Figure sections as 2A and 2B and so on. References to these Figures throughout the specification should be amended accordingly.

(c) The use of the trademarks in the instant specification has been noted in this

application. For example, see page 14, lines 3 and 4: "Tween 20". It is suggested that Applicants examine the whole specification to make similar corrections to the trademarks, wherever trademarks appear.

Rejection(s) under 35 U.S.C § 102 / 103(a)

7) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (e) The invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

8) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person. having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

9) Claims 1-4, 6 and 15-18 are rejected under 35 U.S.C § 102(b) as being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as being unpatentable over Jackson *et al.* (*Ann. N. Y. Acad. Sci.* 730: 217-234, 1994).

Jackson *et al.* teach soluble protein antigens encapsulated in poly D-L-lactide-co-glycolide microspheres having a particle size in the range of 1-10 μM (inclusive of a size of less than 3 μM or 5 μM). Microsphere preparations exhibiting greater than 85% of particles in the range of 1-10

μM are taught (see pages 228, 229 and 231). The encapsulated antigen is tetanus toxoid. The preparation is in a phosphate buffer (i.e., pharmaceutically acceptable carrier). Approximately 100 micrograms (i.e., pharmaceutically effective amount) of the same was injected subcutaneously to a subject, which elicited a Th1-type immune response.

If Jackson's microspheres are viewed as not encompassing at least 50% of the microparticles that are less than 3 μM or 5 μM in size, then it would have been *prima facie* obvious to one of ordinary in the art at the time the invention was made to modify or optimize, by routine experimentation, the percent content of microparticles that are less than 3 μM or 5 μM, in Jackson's microshere composition, such that it contains at least 50% of microparticles that are less than 3 μM or 5 μM in size, to produce the instant invention, with a reasonable expectation of success. The optimization of the percent concentration, in Jackson's composition, of the microparticles that are less than 5 μM is well within the realm of routine experimentation. Since the prior art has already disclosed the use of greater than 85% of microparticles in the range of 1-10 μM, adjusting or optimizing the percent microsphere concentration to the desired level would have been accomplished by routine experimentation.

Claims 1-4, 6 and 15-18 are anticipated by, or in the alternative, as being obvious over Jackson *et al.*

Rejection(s) under 35 U.S.C. § 103

10) Claims 5 and 19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Jackson *et al.* (*Ann. N. Y. Acad. Sci.* 730: 217-234, 1994) as applied to claims 1 and 15 above, and further in view of Mills *et al.* (*Infect. Immun.* 61: 399-410, 1993).

The teachings of Jackson *et al.* are described above, which do not disclose the use, in their method, of microparticles of the recited size comprising a *B. pertussis* antigen.

However, the critical role of Th1 immune response in protective immunity to whooping cough and the need for induction of such a response to *B. pertussis* antigen(s) is well known in the art. For instance, Mills *et al.* teach *B. pertussis* antigen(s) and the need for inducing cellular immune responses mediated by Th1 cells to elicit protective immunity to *B. pertussis* infection (see 'Materials and Methods' and first paragraph under 'Discussion').

Given the combined teachings of Jackson *et al.* and Mills *et al.*, it would have been *prima facie* obvious to one of ordinary in the art at the time the invention was made to replace Jackson's tetanus toxoid antigen with Mills' *B. pertussis* antigen to produce the instant invention, with a reasonable expectation of success. One skilled in the art would have been motivated to produce the instant invention for the expected benefit of inducing a Th1 immune response to a *B. pertussis* antigen in order to elicit Th1 cellular protective immunity to *B. pertussis* infection, since the art has recognized the critical need for inducing a Th1 protective immune response in *B. pertussis* infection as explicitly taught by Mills *et al.*

Claims 5 and 19 are *prima facie* obvious over the prior art of record.

11) Claims 1-6 and 15-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Tice *et al.* (US 6,024,983) or Cahill *et al.* (*Vaccine* 13: 455-462, 1995).

The reference of Tice *et al.* is used in this rejection, because it qualifies as prior art under subsection (e) of 35 U.S.C. § 102 and accordingly is not disqualified under U.S.C. 103(a).

Tice *et al.* disclose a method of administering to a subject subcutaneously, intramuscularly or intraperitoneally, microspheres encapsulated with a staphylococcal enterotoxoid (i.e., an antigen) to elicit a systemic IgG anti-toxin response. See Examples 1 and 2. The microparticles contain poly(DL-lactide-co-glycolide) having a size less than approximately 10 micrometers (see abstract). It is taught that a higher proportion of less than 2 micrometer microcapsules relative to 2-5 micrometer microcapsules migrate to the tissue with greatest efficiency and that microcapsules >5 micrometers in diameter do not enter the mesenteric lymph nodes and spleen (see column 10, section 2). Tice *et al.* disclose the advantages of using DLPG microspheres <10 micrometers in diameter by teaching that microspheres <10 micrometers in size have extremely strong adjuvant activity due to their efficient loading of antigen into accessory cells, which direct the delivery of the microencapsulated antigen into the draining lymph nodes. Tice *et al.* disclose that while >10 micrometers DLPG microspheres remain localized at the site of injection, <10 micrometers microspheres are efficiently phagocytosed and transported by macrophages into the draining lymph nodes (see column 17, lines 7-16). Tice *et al.* expressly teach the advantages of small microcapsules by stating that small microcapsules "preferably less than 5 micrometers, or more preferably 1 to 5 micrometers, potentiate the primary response (without the need of an

adjuvant) because the small microcapsules are efficiently recognized and taken up by macrophages" (see column 17, last paragraph). Thus, Tice *et al.* expressly disclose that the use of small microcapsules, preferably 1 to 5 micrometers which get engulfed by macrophages, obviate the need for immunopotentiators (see column 22, second full paragraph). Improved vaccines comprising antigens encapsulated in these biodegradable microspheres are taught. The antigens that are used for encapsulation can be antigens from *Staphylococcus*, *Haemophilus influenzae* or *Bordetella pertussis* (see abstract; claims 12, 25 and 38; and column 6, lines 30-39). The bioactive agents comprises an antigen or antigens (i.e., more than one antigen) (see claims). The microparticles are prepared using a solvent and solvent evaporation process (see column 7).

Cahill *et al.* disclose a vaccine comprising a solution of filamentous haemagglutinin antigen incorporated in biodegradable poly(DL-lactide-co-glycolide) microparticles approximately 1 micrometer (i.e., < 3 or 5 micrometers) in size and a method of intraperitoneally administering the same to a subject for induction of Th1 immune response to the antigen. The microparticles are prepared using a solvent evaporation method (see abstract; page 456, right column; and page 461).

Tice *et al.* or Cahill *et al.* are silent about the percent composition of microparticles less than 3 or 5 micrometers in size being at least 50%.

However, it would have been *prima facie* obvious to one of ordinary in the art at the time the invention was made to modify, adjust or optimize, by routine experimentation, the percent content of microparticles that are less than 3 μM or 5 μM, in Tice's microsphere composition and Tice's method, such that it contains at least 50% of microparticles that are less than 3 μM or 5 μM in size, to produce the composition and the method of the instant invention, with a reasonable expectation of success. The optimization of the percent concentration, in Tice's or Cahill's composition, of microparticles that are less than 3 μM or 5 μM is well within the realm of routine experimentation and would have been obvious to a skilled artisan.

Claims 1-6 and 15-19 are *prima facie* obvious over the prior art of record.

12) Claim 20 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Tice *et al.* (US 6,024,983) as applied to claim 15 above, and in view of Jones *et al.* (*J. Biotechnol.* 44: 29-36,

1996).

The teachings of Tice *et al.* are explained above which do not disclose a vaccine composition having microparticles comprising at least two subpopulations of microparticles comprising different antigens.

However, the concept of using combined PLG encapsulated antigens is known in the art. Jones *et al.* teach that it is possible to combine vaccine components by individually mixing PLG encapsulated antigens. Jones *et al.* teach that this might overcome the problems of perturbations in the immune responses that have been observed during the development of combination vaccines for the simultaneous administration of immunogens from the same syringe. Jones *et al.* teach that combination vaccines comprising any number of antigens could be tailored to meet any requirement (see page 30). Jones *et al.* further disclose that formation of antigens in polymers of different compositions and therefore, different decay rates would have the effect of programming primary and secondary doses into a single administration. Jones *et al.* teach the application of PLG microencapsulation of antigens for combination of vaccine components and state that combination of vaccines comprising any number of antigens could be tailored to meet any requirement (see page 30, right column).

It would have been *prima facie* obvious to one of ordinary in the art at the time the invention was made to use two subpopulations of Tice's microparticles and entrap more than one antigen in the microparticles to produce the instant invention, with a reasonable expectation of success, because Jones *et al.* expressly teach that PLG microcapsules comprising any number of antigens can be combined to produce encapsulated combination vaccines. One skilled in the art would have been motivated to produce the instant invention for the expected benefit of effectively and advantageously programming primary and secondary doses having different decay rates in a single composition.

Claim 20 is *prima facie* obvious over the prior art of record.

Relevant Prior Art

13) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicant's disclosure:

- Eldridge *et al.* (*J. Controlled Release* 11: 205-214, 1990) disclose a method of

oral administration of biodegradable poly(DL-lactide-co-glycolide) microspheres ≤ 10 μm in diameter containing a toxoid vaccine of staphylococcal enterotoxin B (see title and abstract). At days 1, 2 and 4, 76-82% of ≤ 5 μm microparticles remained constant. The microspheres which were observed to penetrate deep into the Peyer's patches were almost exclusively ≤ 5 mm in diameter. No microspheres >5 μm in diameter were ever observed to enter the spleen (see page 209, right column). Figure 3 shows that approximately equal parts of a toxoid-containing microspheres are contained in microcapsules above and below 5 μm in diameter. Microspheres ≤ 5 μm would be predicted to induce a predominantly circulating antibody response based on their propensity to disseminate to systemic lymphoid tissues within antigen presenting accessory cells (see page 213, right column).

- Shahin *et al.* (*Infect. Immun.* 63: 1195-1200, 1995) teach a method of inducing protective immunity in a subject by subcutaneously administering an antigen from *Bordetella pertussis* encapsulated in poly(DL-lactide-co-glycolide) microspheres. A method of intranasally administering a combination of three *Bordetella pertussis* antigens encapsulated in poly(DL-lactide-co-glycolide) microspheres (see entire document).

- Cahill *et al.* (*Vaccine* 13: 455-462, 1995) teach that induction of Th1-mediated cellular immune response is the key factor in acquired immunity to *Bordetella pertussis* infection (see entire document).

- Jones *et al.* (*Vaccine* 13: 675-681, 1995) teach a vaccine comprising the *Bordetella pertussis* fimbrial antigen encapsulated in 11-40 micrometer poly(DL-lactide-co-glycolide) microspheres prepared by solvent evaporation method. A method of intraperitoneally administering the vaccine to a subject to elicit a substantial systemic immune response is taught (see entire document).

- O'hagan (*J. Pharm. Pharmacol.* 49: 1-10, 1997) teach that microparticles prepared from biodegradable microparticles of defined dimensions, for example, <5 micrometers, act as effective vaccine adjuvants (see abstract). On systemic administration, smaller PLG microparticles of <10 micrometer size are significantly more immunogenic than >10 micrometer microparticles and exert an adjuvant effect for cell-mediated immunity including the induction of

cytotoxic T-cell responses after both systemic and mucosal administration (see page 6).

- Jones *et al.* (*J. Biotechnol.* 44: 29-36, 1996) teach that PLG can be processed as microspheres in a range of sizes including those optimal for uptake by macrophages or other antigen presenting cells (see page 30, left column).

Remarks

14) Claims 1-6 and 15-20 stand rejected.

15) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week.

16) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SD

S. Devi, Ph.D.
Patent Examiner
June 2001